REMARKS

Applicants gratefully acknowledge withdrawal of the previous 35 U.S.C. § 112, second paragraph rejections of claims 10-11 and 15-16. Applicants are filing this response along with a Request for Continued Examination (RCE). The Examiner has maintained the previous 35 U.S.C. § 102(b) and § 103(a) rejections. Applicants traverse these rejections and respectfully request the Examiner to reconsider the rejections in view of the following remarks.

The 35 U.S.C. § 102(b) Rejection of claims 1-2, 5-6 and 9-11

Claims 1-2, 5-6 and 9-11 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Carpino et al. (WO 97/24369, hereinafter the '369 reference; and WO 98/58947, hereinafter the '947 reference). Applicant respectfully traverses the 35 U.S.C. § 102(b) rejection of claims 1-2, 5-6 and 9-11.

The Examiner has stated, and applicant agrees, that the instant invention provides a method of *stimulating or increasing appetite* using growth hormone secretagogues of formula I or IA alone or in combination with GHRP-6, GHRP-1, GHRP-2, hexarelin, IGF-I or IGF-II. The '369 and '947 references disclose the use of certain growth hormone secretagogues alone or in combination with GHRP-6, GHRP-1, hexarelin, IGF-I or IGF-II for the treatment of medical disorders associated with deficiency in growth hormone such as, *inter alia*, *obesity* in a human. The Examiner then alleged that the present method of stimulating or increasing appetite using growth hormone secretagogues of formula I or IA alone or in combination with GHRP-6, GHRP-1, GHRP-2, hexarelin, IGF-I or IGF-II is inherently anticipated by the '369 and '947 references as the method steps are the same and the amount of compound used is the same. The Examiner also alleged that claiming a new use, new function or unknown property which is inherently present in the prior art does not make the claim patentable.

Applicant submits that the present method of *stimulating or increasing appetite* using growth hormone secretagogues of formula I or IA alone or in combination with GHRP-6, GHRP-1, GHRP-2, hexarelin, IGF-I or IGF-II is not anticipated by the '369 or '947 references. The fact that from a manipulative point of view what is claimed is exactly the same as what was done in the prior art is not determinative of the patentability of a process directed to a new use. Other factors, including the material being treated, must be given weight. *Ex parte Garbo* (POBA 1955) 108 USPQ 379. The discovery of a new use of an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957); and MPEP 2112.02. Also, for a prior art reference to anticipate a claim, the reference must

disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art. Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there. *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 43 USPQ 2d 1481, 1490 (Fed. Cir. 1997).

The '369 and '947 references do not disclose or suggest the use of the growth hormone secretagogues in a method of *stimulating or increasing appetite*. The point of novelty of the instant claims is the "method for *stimulating or increasing appetite* in a patient" using the compounds of formula I or IA. Under *Ex parte Garbo* reasoning, the fact that the instant method steps are the same as the method steps in the '369 and '947 references is not determinative of the patentability of the instantly claimed method. In other words, the fact that the same amount of growth hormone secretagogue of formula I or IA is administered in the instant new method of treatment as was administered in the methods of the '369 and '947 references does not render the instant new method of treatment as anticipated. Furthermore, the '369 and '947 references do not disclose a method of *stimulating or increasing appetite* using the growth hormone secretagogues of formula I and IA. Therefore, under *Motorola, Inc. v. Interdigital Tech. Corp.* reasoning, the instantly claimed method of stimulating or increasing appetite is not anticipated by the '369 and '947 references because these references do not disclose or suggest each and every element of the instantly claimed method of treatment.

The Examiner has further stated that the method of increasing levels of endogenous growth hormone and treating medical disorders would *inherently* stimulate or increase appetite in a patient. The Examiner's inherency argument is based upon the premise that stimulating or increasing endogenous growth hormone with the compounds of formula I necessarily results in the stimulation of appetite in the patient. The Examiner then states that one of ordinary skill in the art would recognize that the mechanism of action of increasing growth hormone results in stimulating appetite based upon the Ankerson et al., Murphy et al.; Ghigo et. Al. and Vaccarino et al. references.

Applicants respectfully disagree with the Examiner's position that increasing endogenous growth hormone levels with a compound of formula I necessarily results in the stimulation of appetite in a patient. An anticipation rejection to be based on inherency requires that the missing element(s) must be a necessary consequence of the prior art. Glaxo Inc. v. Novopharm Ltd., 52 F.3d 1043, 34 U.S.P.Q.2d 1565, 1567 (Fed. Cir. 1995). In Glaxo, the Federal Circuit affirmed the district court's finding that a prior art process for making the drug ranitidine did not inherently anticipate a claim to a particular polymormphic form of ranitidine called Form 2 because the prior art process "could yield crystals of either

polymorph [Form 1 not covered by the claim or Form 2 covered by the claim]." Id. at 1047. The district court expressly found that practicing the prior art process "resulted at times in the exclusive production of Form 1 [not covered by the claim] and at other times in the exclusive production of Form 2 [covered by the claim]." Glaxo Inc. v. Novopharm Ltd., 830 F.Supp. 871, 877 (E.D.N.C. 1993), aff'd, 52 F.3d 1043 (Fed. Cir. 1995) As a result, the district court concluded that "[t]he evidence does not support a finding that Form 2 invariably results from the practice of [the prior art process]." (Id.) In other words, practicing the prior art process sometimes would have produced a product covered by the later patent and sometimes would not have produced a product within the claim. (compare Schering Corp. v. Geneva Pharmaceuticals, 339 F.3d 1373, 1379, 67 U.S.P.Q.2d 1664, 1669 (Fed. Cir. 2003), petition for panel rehearing and rehearing en banc denied, (Fed. Cir. October 28, 2003) where the Court found that a patent claim directed to the metabolite of loratadine was inherently anticipated by a teaching to administer loratadine to patients because the claimed metabolite forms as a necessary result of loratadine administration in all patients; and further compare Eli Lilly and Co. v. Barr Laboratories Inc. 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001) where the Court found that a patent claim directed to a method of inhibiting serotonin reuptake by administration of fluoxetine was inherently anticipated by a method of treating depression by administration of fluoxetine because the administration of fluoxetine necessarily results in the inhibition of serotonin reuptake in all patients.)

The instant facts parallel those in Glaxo because the method of stimulation of appetite in a patient is not a necessary consequence of, or inherent in, the method of increasing endogenous growth hormone in a patient. The Examiner cites to the Ankerson et al., Murphy et al.; Ghigo et. al. and Vaccarino et al. references and concludes that these references teach that increasing endogenous growth hormone in a patient necessarily results in stimulating or increasing appetite in a patient. Applicants respectfully disagree with the Examiner's position that these references teach that increasing endogenous growth hormone in a patient necessarily results in stimulating or increasing appetite in a patient. To the contrary, the Ankerson reference at page 501, right column, lines 1-6 states that some growth hormone secretagogues are not very selective and have an influence on food intake. Ankerson goes on to state that "these actions could take place through activation of specific receptors at levels other than in the hypothalamic-pituitary system." Ankersen then concludes that a large number of growth hormone secretagogues have been identified and that it is unresolved whether these compounds elicit their effect through the same pathway, but with the identification of possibly two receptors and a discrepancy in the potency of different classes of compounds, it seems likely that these compounds do not act in the same way. Likewise, the Murphy reference relates to the specific compound MK-677 and does not

state that growth hormone secretion by all growth hormone secretagogues necessarily results in appetite stimulation. The Ghigo reference also does not state that growth hormone secretion necessarily results in appetite stimulation. The Vaccarino reference pertains to appetite stimulation using GRF, which is a peptide compound that acts on a different receptor than the growth hormone secretagogues employed in the present invention. Since GRF is structurally unrelated to the present growth hormone secretagogues and acts on a different receptor one skilled in the art would not infer from that reference that all compounds that increase growth hormone would stimulate appetite. Applicants also submit that certain studies have indicated that appetite stimulation is related to a mechanism not involving growth hormone release and therefore teach away from the premise that growth hormone release necessarily increases appetite. For example, Torsello, A. et. al in *European Journal of Pharmacology* 360 (1998) 123-129 at page 128, left column, lines 47-56 concluded that certain hexarelin (GHRP) analogs stimulate appetite after systemic administration in the rat; that the stimulation of eating behavior is largely or entirely independent of the effects these compounds have on GH release and that minor variations in the structure of the compound can result in unpredictable variations of the pharmacological profile. A person of ordinary skill in the art would therefore conclude that the question of whether growth hormone secretion necessarily results in appetite stimulation is unresolved. Applicants submit that no inherent anticipation exists because practicing the prior art method of increasing endogenous growth hormone in a patient would not have necessarily resulted in the present method of stimulating appetite in a patient. Furthermore, the patient in the previous method is distinquishable from the patient in the present invention since the patient in the previous method may be in need of increasing growth hormone secretion, such as a GH deficient individual, and not be a patient in need of appetite stimulation.

For these reasons applicant respectfully requests that the Examiner reconsider and withdraw the 35 U.S.C. § 102(b) rejection of claims 1-2, 5-6 and 9-11.

The 35 U.S.C. § 103(a) Rejection of claims 12-16

Claims 12-16 have been rejected under 35 U.S.C. § 103(a) as being obvious over the '369 and '947 references in view of Vaccarino et al. (CA 2095788, hereinafter "Vaccarino") and The Merck Manual of Diagnosis and Therapy (16th Edition) pages 1529-1534 (hereinafter "Merck"). Applicant respectfully traverses the 35 U.S.C. § 103(a) rejections of claims 12-16.

Claims 12-16 are drawn to a method of stimulating or increasing appetite in a patient by employing compounds of formula I or I-A in combination with an antidepressant such as an SSRI, MAO or atypical antidepressant. The Examiner has acknowledged, and applicant agrees, that the '369 and '947 references do not disclose a method of stimulating or

increasing appetite by administering a compound of formula I or I-A and an antidepressant. The Examiner has stated that Vaccarino discloses that a growth hormone secretagogue or a growth hormone releasing factor is known to be useful in a method of treating appetite disorder or stimulating appetite in a patient. The Examiner has also stated that Merck discloses that an antidepressant is known to be useful for stimulating or increasing appetite in a patient. The Examiner has then stated that one of ordinary skill in the art would have been motivated to employ the compounds of formula I and IA in combination with an antidepressant since both growth hormone secretagogues and antidepressants are known to be useful in a method of stimulating or increasing appetite in a patient.

Applicant submits that one of ordinary skill in the art, in view of the combination of the '369, '947, Vaccarino and Merck references, would not have found the present method of treatment of claims 12-16 to be obvious at the time of invention. When analyzing prior art "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Applicants submit that the combined references do not disclose or suggest a method of *stimulating or increasing appetite* using a combination of a growth hormone secretagogue of formula I or I-A and an antidepressant.

First, the abstract at page 1 of each of the '369 and '947 references disclose a method of treating *obesity* using the compounds of formula I and IA and, in that respect, teach away from a method of *increasing or stimulating appetite* using the compounds of formula I and IA, since the treatment of obesity would require *appetite suppression*, rather than *appetite stimulation*.

Second, page 4, line 32 through page 5, line 8 of Vaccarino discloses that GRF, fragments and derivatives thereof are useful for stimulating appetite in a patient and page 7, lines 4-26 of Vaccarino describe that GRF is a 44 amino acid from human pancreatic tumor. The Vaccarino reference does not disclose or suggest that any other growth hormone secretagogue, such as the compounds of formula I and I-A, are useful for increasing or stimulating appetite. Applicant further submits that the compounds of formula I and IA are distinct from and not suggested by the GRF, fragments and derivatives thereof described in Vaccarino. It has also been shown by Torsello, A. et. al in *European Journal of Pharmacology* 360 (1998) 123-129 at page 128, left column, lines 47-56 that certain hexarelin (GHRP) analogs stimulate appetite after systemic administration in the rat; that the stimulation of eating behavior is largely or entirely independent of the effects these compounds have on GH release and that minor variations in the structure of the compound can result in unpredictable variations of the pharmacological profile. Applicants submit that one of ordinary skill in the art, in full consideration of the relevant art, would not extrapolate

the teaching of Vaccarino and conclude that all compounds that increase endogenous growth hormone would stimulate appetite. In fact, one skilled in the art could readily conclude that compounds that increase endogenous growth hormone may or may not stimulate appetite, and if the compound does stimulate appetite it may do so by a mechanism entirely independently of growth hormone release. Therefore, one of ordinary skill in the art, prior to the present invention, would not have found it obvious to use the compounds of formula I and IA in a method of increasing or stimulating appetite.

Third, Merck indicates that antidepressants can be used to treat depression and thereby alleviate its symptoms of anorexia or decreased appetite. However, Merck at page 1533, column 2, lines 10-12 also discloses that antidepressants, such as an SSRI, can cause anorexia in some patients in the first few months of treatment. Clearly, for those patients, the antidepressant would not be useful for increasing or stimulating appetite and the Merck reference, in this respect, teaches away from instant claims 12-16.

One of ordinary skill in the art would not be motivated to use a combination of a compound of formula I or I-A with an antidepressant in the present method of treatment since the cited references simply do not suggest such a method. There is no motivation for the instantly claimed method since the '369, '947 and Merck references each, at least in part, teach away from the instant method as claimed. Furthermore, Vaccarino does not suggest or provide motivation to one of ordinary skill in the art for the present method of treatment because the growth hormone secretagogues of formula I and I-A are distinct from, not equivalent to and not suggested by the GRF, fragments and derivatives thereof employed in Vaccarino. Furthermore, one skilled in the art would appreciate that appetite stimulation can be the result of a mechanism entirely independent of growth hormone secretion and that minor structural variation can result in loss of pharmacological activity as described in the Torsello et al. reference as described hereinabove. Therefore, one of ordinary skill in the art in possession of the '369, '947, Vaccarino and Merck references, prior to the present invention, would not have found it obvious to arrive at the instant method of claims 12-16. For these reasons applicant respectfully requests the Examiner to reconsider and withdraw the 35 U.S.C. § 103(a) rejections of claims 12-16.

The 35 U.S.C. § 103(a) Rejection of claims 17-20

Claims 17-20 have been rejected under 35 U.S.C. § 103(a) as being obvious over the '369 and '947 references in view of Vaccarino, Merck and The Pharmacological Basis of Therapeutics (1996) page 928-932 and 339-430 (hereinafter "PBT"). Applicant respectfully traverses the 35 U.S.C. § 103(a) rejections of claims 17-20.

Claims 17-20 are drawn to a method of stimulating or increasing appetite in a patient by employing compounds of formula I or I-A in combination with an antiemetic or

antipsychotic. The Examiner has acknowledged, and applicant agrees, that the '369 and '947 references do not disclose a method of stimulating or increasing appetite by administering a compound of formula I or I-A and an antiemetic or antipsychotic. The Examiner has stated that Vaccarino discloses that a growth hormone secretagogue or a growth hormone releasing factor is known to be useful in a method of treating appetite disorder or stimulating appetite in a patient. The Examiner has also stated that Merck and PBT disclose that an antiemetic or antipsychotic is known to be useful in treating decreasing appetite or anorexia in depression. The Examiner has then stated that one of ordinary skill in the art would have been motivated to employ the compounds of formula I and IA in combination with an antiemetic or antipsychotic since both growth hormone secretagogues and an antiemetic or antipsychotic are known to be useful in a method of stimulating or increasing appetite in a patient.

Applicant submits that one of ordinary skill in the art, in view of the combination of the '369, '947, Vaccarino, Merck and PBT references, would not have found the present method of treatment of claims 17-20 to be obvious at the time of invention. When analyzing prior art "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Applicants submit that the combined references do not disclose or suggest a method of stimulating or increasing appetite using a combination of a growth hormone secretagogue of formula I or I-A and an antiemetic or antipsychotic.

First, the abstract at page 1 of each of the '369 and '947 references disclose a method of treating *obesity* using the compounds of formula I and IA and, in that respect, teach away from a method of *increasing or stimulating appetite* using the compounds of formula I and IA, since the treatment of *obesity* would require *appetite suppression*, rather than *appetite stimulation*. Applicant submits that prior to the present invention the compounds of formula I and IA as disclosed in the '369 and '947 references were not known to be useful for increasing or stimulating appetite. Second, page 4, line 32 through page 5, line 8 of Vaccarino discloses that GRF, fragments and derivatives thereof are useful for stimulating appetite in a patient and page 7, lines 4-26 of Vaccarino describe that GRF is a 44 amino acid from human pancreatic tumor. The Vaccarino reference does not disclose or suggest that any other growth hormone secretagogue, such as the compounds of formula I and I-A, are useful for increasing or stimulating appetite. Applicant further submits that the compounds of formula I and IA are distinct from and not suggested by the GRF, fragments and derivatives thereof described in Vaccarino. Furthermore, one skilled in the art would appreciate that appetite stimulation can be the result of a mechanism entirely independent of

growth hormone secretion and that minor structural variation can result in loss of pharmacological activity as described in the Torsello et al. reference as described hereinabove. Therefore, one of ordinary skill in the art, prior to the present invention, would not have found it obvious to use the compounds of formula I and IA in a method of increasing or stimulating appetite.

One of ordinary skill in the art would not be motivated to use a combination of a compound of formula I or I-A with an antiemetic or antipsychotic in the present method of treatment since the cited references simply do not suggest such a method. There is no motivation for the instantly claimed method since the '369 and '947 references at least in part, teach away from the instant method as claimed. Furthermore, Vaccarino does not suggest or provide motivation to one of ordinary skill in the art for the present method of treatment because the growth hormone secretagogues of formula I and I-A are distinct from, not equivalent to and not suggested by the GRF, fragments and derivatives thereof employed in Vaccarino. Therefore, one of ordinary skill in the art in possession of the '369, '947, Vaccarino, Merck and PBT references, prior to the present invention, would not have found it obvious to arrive at the instant method of claims 17-20. For these reasons applicant respectfully requests the Examiner to reconsider and withdraw the 35 U.S.C. § 103(a) rejections of claims 17-20.

The Examiner has also stated that all active composition components herein are known to be useful to *stimulate or increase appetite* and therefore the claimed invention as a whole is clearly prima facie obvious over the prior art under *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980). Applicant submits that prior to the present invention the compounds of formula I and IA were not known to be useful in a method of *increasing or stimulating appetite* as discussed above and therefore all active composition components were not known to be useful for *increasing or stimulating appetite*. Therefore, Applicant respectfully submits that under *In re Kerkhoven* reasoning and in light of applicant's comments above, the instant invention is not prima facie obvious.

Applicant, having addressed all points and concerns raised by the Examiner, believes that the application is in condition for allowance and respectfully requests an early and favorable action in light of the foregoing amendment and remarks.

Respectfully submitted,

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